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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/820,975	04/07/2004	Daniel Santi	020547-003700US	9532
81228	7590	03/16/2009	EXAMINER	
Fox Rothschild LLP			POPA, ILEANA	
Bristol-Myers Squibb				
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/820,975	SANTI ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	ILEANA POPA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 02 December 2008.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-19 and 31-39 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-19 and 31-39 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)          | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

### **DETAILED ACTION**

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office action.

2. Claims 20-30 have been cancelled. Claims 1, 2, 14, 19, 35, and 39 have been amended.

Claims 1-19 and 31-39 are pending and under examination.

3. All rejections pertaining to claim 20 are moot because Applicant cancelled the claim in the reply filed on 12/02/2008.

The rejection of claim 1 under 35 U.S.C. 102(b) as being anticipated by Hodgson (PGPUB 2002/0025561) is withdrawn in response to Applicant's amendments to the claims filed on 12/02/2008. Specifically, Applicant amended the claims to recite that the ligatable fragments are not purified prior to ligation is not taught by Hodgson.

The rejection of claims 1-19 and 31-39 under 35 U.S.C. 103(a) as being unpatentable over Hodgson, in view of each Slater et al. (PGPUB 2005/0074883), Gokhale et al. (Science, 1999, 284: 482485), and Santi et al. (PGPUB 2004/0166567) is withdrawn because Applicant submitted 131 and 132 Declarations disqualifying Slater et al. (PGPUB 2005/0074883) and Santi et al. (PGPUB 2004/0166567) as prior art. The Declarations were filed on 12/02/2008.

***New Rejections***

***Claim Rejections - 35 USC § 103***

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

5. Claims 1-19 and 31-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hodgson (PGPUB 2002/0025561, of record), in view of each Padgett et al. (Gene, 1996, 168: 31-35), Resnick et al. (WO 98/01573), and Gokhale et al. (Science, 1999, 284: 482485, of record).

Hodgson teaches a method of obtaining a synthetic gene by ligating three DNA segments, the method comprising: **(a)** providing three different DNA vectors each comprising a selectable marker and a different DNA insert, wherein all DNA inserts are flanked by identical type IIS restriction sites, **(b)** cleaving each DNA vector with a type IIS enzyme to generate segments with region of identity (or ligatable ends) with an adjacent segment, **(c)** simultaneously ligating the three DNA segments, and selecting the ligation product based on the presence in the vector of the selectable marker; one or more of the DNA segments could comprise the vector and the final ligation product is a complete recombinant DNA/vector, which could be made either linear or circular (i.e., the final ligation product comprises a selection marker from one of the three vectors), and **(d)** transforming cells with the final ligation product and selecting the transformants

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comprising the ligation product based on the presence of the selection marker above (claim 1) (p. 3, paragraphs 0030 and 0031, claims 1, 5, 9, and 10). It is noted that, in order to assemble the gene from the three different DNA segments, the three different segments must be assembled in the correct order, i.e., each of the end DNA segments must necessarily comprise one region of identity (ligatable end) with the internal segment; therefore, in order to be both end DNA fragments, the internal segment must necessarily comprise two regions of identity (ligatable ends). Since Hodgson teaches that the three inserts are flanked by identical type IIS restriction sites; therefore, the first and third cleavage sites are identical, the second and fourth cleavage sites are identical, and the 5' and 3' cleavage site in the same or two different Type 3 DNA molecules are identical (claims 2, 7-10, 14, 16-19). Hodgson also teaches and that cleavage with type IIS enzymes generates three segments with region of identity (or ligatable ends) with the adjacent segment; therefore, cleavage of the second site produces a single-stranded overhang in the in the first segment which is ligatable to a single-strand overhang of an adjacent segment, cleavage of the fourth site produces a single-stranded overhang in the in the second segment which is ligatable to a single-strand overhang of an adjacent segment, while cleavage at the 5' and 3' sites in the third fragment produces 5' and 3' single-strand overhands which are ligatable to the single-strand overhangs of two adjacent fragments (claim 14). Additionally, Hodgson teaches that one or more of the DNA segments could comprise the vector (see above), i.e., the resulting linear first and second DNA molecule comprise the DNA segments covalently associated with the vectors having the selectable markers (claim 35).

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Hodgson does not teach ligating the digested DNA segments without purifying the digested fragments (claims 1, 2, 14, and 35). However, at the time the invention was made, ligating digested fragments without purifying them was taught by the prior art; the prior art also taught that the presence of the type IIS restriction endonuclease in the ligation reaction reduces the cloning time and provides selection for the desired ligation product (see Padgett et al., p. 34, column 1; p. 35, column 1). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the Hodgson's method by eliminating the purification step after digestion, with a reasonable expectation of success. One of skill in the art would have been motivated to do so in order to simplify the procedure and select for the desired ligation product. One of skill in the art would have been expected to have a reasonable expectation of success because the prior art teaches that such a simplified ligation procedure can be successfully used to obtain the desired product.

Hodgson and Padgett et al. do not each vector as comprising a selectable and counter selectable marker, with each vector comprising a distinct set of selectable and counter selectable markers (claims 2-10, 13-19 and 31-39). However, at the time the invention was made, the prior art taught the use of a combination of vectors each vector having a distinct set of selectable and counter selectable markers for the accurate selection of the final recombinant product comprising the desired insert, wherein the selectable marker could be the tetracycline resistance gene and the counter selectable marker could be the *ccdB* or *SacB* gene (see Resnick et al., p. 10, lines 9-15, p. 11, lines 24-26, p. 20, lines 9-30, p. 21, lines 15-25, p. 23, lines 23-28, p. 35, lines 20-26;

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Stewart et al., column 15, lines 34-65, column 18, lines 7 and 8, column 19, lines 35-48). One of skill in the art would have known to use the right combination of selectable and counter-selectable markers for a more efficient selection of the desired product.

One of skill in the art would have also known to use selection based on the presence of both the first and the second selectable markers when cleaving the DNA vectors such as to obtain two of the DNA segments covalently attached to the vector to ensure that both segments are present in the final ligation product.

Hodgson, Padgett et al., Resnick et al., and Stewart et al. do not teach PKS (claims 11 and 12). Gokhale et al. teach recombining modules from the naturally-occurring PKSs (p. 482, column 2). It would have been obvious to one of skill in the art, to use the method of Hodgson, Padgett et al., Resnick et al., and Stewart et al. to obtain diverse synthetic PKSs as taught by Gokhale et al., with a reasonable expectation of success. The motivation to do so is provided by Gokhale et al. who teach PKSs have a modular structure, and novel combinations of modules could result the synthesis of diverse medicinally important new products (Abstract, p. 482, column 1). One of skill in the art would have been expected to have a reasonable expectation of success in making such synthetic genes because Hodgson teach the successful *in vitro* synthesis of genes by his method.

It is noted that the instant specification defines Type I, II, and III vectors as vectors containing an insertion site for the DNA segment and selectable markers, wherein the only difference between the Type I, II, and III vectors is that each contains a different the selectable marker as compared to the others (see p. 19, paragraph 0230).

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Therefore, by using a method according to the combined teachings of Hodgson, Padgett et al., Resnick et al., and Stewart et al., and Gokhale et al. (i.e., employing different selectable and/or counter selectable markers on each vector), one of skill in the art would use Type I, II, and III molecules.

With respect to the limitation of the presence of at least two Type 3 DNA molecules (claims 15 and 18), it is noted that the Type 3 DNA molecules contain the interior segments. One of skill in the art would know to use more than one Type 3 DNA molecule, depending on the need to add more modules to the synthetic gene, especially that Hodgson teaches his method as being suitable to be used with multiple internal segments (p. 3, paragraph 0031). With respect to claim 4, one of skill in the art would have been motivated to isolate the final ligation product from the transformants in order to sequence or transfer it to another vector, as needed; it is noted that such isolation is routine in the art.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant's arguments are answered below to the extent that they pertain to the instant rejection.

Applicant argues that, by teaching purifying their digested segments, Hodgson teaches away from using counter selection markers because one of skill in the art would have figured out that counter selection markers are not needed in Hodgson's method. Applicant also argues that Gokhale et al. do not cure Hodgson's deficiencies.



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Applicant's arguments are acknowledged however, they are not found persuasive because the instant rejection is an obviousness-type rejection based on a combination of references and not on Hodgson alone, which combination teaches ligation without segment purification and the necessity of using selectable and counter selectable markers to select the ligation product. With respect to Gokhale et al., again, it is the combination of Hodgson, Padgett et al., Resnick et al., and Stewart et al. which teaches the claimed invention and therefore, Gokhale et al. have nothing to remedy. The reference was only cited for teaching the limitations of claims 11 and 12, limitations not taught by Hodgson, Padgett et al., Resnick et al., and Stewart et al. With respect to the filed Declaration stating that the use of two-marker vectors makes selection more efficient, it is noted that such was well known in the art at the time the invention was made (see above).

6. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ileana Popa/  
Examiner, Art Unit 1633